wherein an anti-LTNF comprising an antibody made

(1) against natural LTNF, or

(2) against a synthetic peptide consisting of at least five amino acids of the sequence

Leu Lys Ala Met Asp Pro Thr Pro Pro Leu Trp Ile Lys Thr Glu

is used as a reagent for the ELISA tests and reacts with free toxin in both the first test and the second test,

wherein the numerical assay values in both the first test and the second test are given by ELISA color assay for anti-LTNF, and

wherein an anti-serum having a higher neutralizing index is indicative of a greater potency for that anti-serum against a given toxin.

Remarks

Status of claims

Claims 5 and 7-16 are pending and under final rejection. It is proposed to amend claims 7, 8 and 9 as shown above for compliance with 35 USC 112, or alternatively, to place the claims in better form for appeal. This is the first opportunity for applicant to respond to the grounds of rejection as stated for claims 7, 8 and 9 and the amendment was therefore not made earlier.

Detailed discussion

35 USC 112 rejections

Claim 7

Claim 7 is rejected as vague and indefinite on the basis of the recitation "conducting an ELISA binding or ELISA titer." This rejection is traversed but is obviated by the present amendment.

Claim 7 is amended to recite that:

> "wherein the anti-LTNF and the toxin are brought together in a procedure wherein the anti-LTNF is in a fluid state and the toxin comprises a lethal toxin which is attached to a plate, to produce the product capable of being detected by ELISA"

followed by the step of:

> "conducting an ELISA color assay on the product of the immunological reaction."

The claim is more clear as amended, and is submitted to be in compliance with 35 USC 112. The ELISA test is used in a non-traditional way in the invention, as it is measuring an immunological reaction between an antibody (anti-LTNF) and an antigen (toxin) against which the antibody is not specific. Reconsideration and withdrawal of the rejection is therefore requested.

Claim 8

Claim 8 is rejected for indefiniteness for the recitation of food. It is stated that food encompasses both liquids and solids. This aspect of the rejection is traversed. Claim 8 recites: "...toxin is contained in a fluid selected from the group consisting of food,...". Claim 8 only encompasses fluid forms of food and the stated basis for the rejection therefore does not apply. Reconsideration of this aspect of the rejection is therefore requested. It is further stated: "Applicant has not shown how biological toxin is obtained from food." This aspect of the rejection is traversed. Example 5 show the detection of BoTx in dairy milk. Reconsideration of this aspect of the rejection is therefore requested. Reconsideration and withdrawal of the 35 USC 112 rejection of claim 8 is therefore requested.

Claim 8

Claim 8 is further rejected as vague and indefinite on the basis of the recitation of "second antibody". The rejection is traversed but is obviated by amendment of the claim to delete reference to "second antibody". Reconsideration is requested.

Claim 9

Claim 9 is rejected as vague and indefinite on the basis that the method is for determining neutralizing potency but there is no step in the method to indicate how that is achieved. The rejection is traversed but is obviated by amendment of the claim to delete reference to the "neutralizing potency" terminology. Reconsideration of this aspect of the rejection is requested. Claim 9 stands further rejected on the basis that it is said to be unclear as to how free toxin is being measured. This rejection is traversed, but is submitted to be obviated by the amendment to claim 9, which now employs "first test", "second test" terminology, as well as the recitation of a color assay to determine anti-LTNF.

Claim 9 is directed toward a process as described in Example VI in which venom toxins from various species of snakes were mixed with normal serum or with respective specific anti-serum. The mixtures were incubated at 37° C for 1 hr. to permit neutralization of the toxin by its specific anti-serum. In Example VI, the free toxin (i.e., toxin which has not been neutralized by its antitoxin) is detected in the same manner as in the earlier examples, such as Example II, and this is stated in Example VI. In Example VI, the anti-LTNF utilized in both tests reacts immunologically with the free toxin, but not with neutralized toxin. Coloration will therefore track the amount of toxin reacted by anti-LTNF remaining on the plate, and thus provide an indication of the amount of toxin which was not neutralized by the specific antitoxin. A large difference in coloration between the two tests means that a lot of toxin was neutralized by the specific anti-toxin, and that the specific anti-toxin is therefore highly potent.

Claim 8 as amended for greater clarity recites:

> "wherein an anti-LTNF...
> is used as a reagent for the ELISA tests and reacts with free toxin in both the first test and the second test,
> wherein the numerical assay values in both the first test and the second test are given by ELISA color assay for anti-LTNF..."

The claim should therefore now be clear as to how the complexes are being distinguished from each other. It should also now be more clear that the lesser the free toxin in the complex, the greater the neutralization index as determined by the test.

Reference to the amount of normal serum employed in the first test has been deleted as it is not critical to the validity of the tests.

The claim as amended thus recites a bioassay step which leads to an indication of antivenom potency. Reconsideration of the 35 USC 112 rejection of claim 9 is therefore requested.

35 USC 102 rejection

Claims 5 and 7-16 stand rejected under 35 USC 102(e) over Lipps et al., US 5,744,449, issued April 28, 1998. This rejection is traversed. The office action quotes the applicable part of the statute as:

"A person shall be entitled to a patent unless--
(e) the invention was described in a patent granted on an application for patent **by another** filed in the United States before the invention thereof by the applicant for patent,..." (emphasis added).

The inventors in the instant application are Binie V. Lipps and Frederick W. Lipps. The inventors in US 5,744,449 are Binie V. Lipps and Frederick W. Lipps, which is identical. The issued patent is therefore not "by another". Reconsideration and withdrawal of the 35 USC 102(e) rejection is requested.

Attachment

Attached hereto is a marked up version of the changes made by the current amendment by bracket and underline method. The attachment is captioned "Version with markings to show changes made". Support for the changes are pointed out in the comment which follows if deemed necessary.

Conclusion

In view of the forgoing amendments and arguments, reconsideration and withdrawal of all grounds of rejection and early notice of allowance is respectfully solicited.

Respectfully submitted,

10-30-01

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 7 is amended as follows:

7. (thrice amended) A process as in claim 5 wherein the anti-LTNF and the toxin are brought together in a procedure wherein the anti-LTNF is in a fluid state and the toxin comprises a lethal toxin which is attached to a plate, to produce the product capable of being detected by ELISA, said process further comprising

conducting an ELISA [binding or ELISA titer] color assay on the product of the immunological reaction, and

~~obtaining a numerical result which is roughly proportional to the~~ lethal dose [toxicity] of the [at least one biological] toxin[.] as determined by animal bioassay.

Support: The amendments are fairly supported by Example II, (page 11, lines 18-32) which states:

"The lethal dose was determined by injecting intraperitoneally 0.1 ml of venom in various concentrations in 20g ICR mice. The wells of the microplate were coated with 0.1 ml of various concentrations of venom as antigen starting from 100 μg to 0.000564 (564 nanogram) diluted threefold in 0.05 M phosphate buffer saline pH 7.4 (PBS) and incubated for overnight at room temperature. After 18 to 24 hours the plate was washed three times (3X) with PBS and the plate was blocked with 0.25 ml/well of 3% Teleostean gelatin from cold water fish (Sigma) for 1/2 hour at RT. The plate was washed 3X with PBS and 0.1 ml/well of 10 μg/ml purified mouse anti-LTNF IgG was added. The plate was incubated at 37°C for 1 to 2 hours. And then, the plate was washed 3X with PBS and horseradish peroxidase conjugated with mouse IgG made in goat was added and incubated for 1 hour at 37°C. After which the plate was washed 3X with PBS and reacted with O Phenylenediamine Dihydrochloride (OPD) for color development. The test was read after 1/2 hour visually or preferably on ELISA plate reader."

Claim 8 is amended as follows:

8. (Amended) A process as in claim 5 wherein the biological toxin is contained in a fluid selected from the group consisting of food, blood sera and other body fluid, saliva, urine and milk, [and urine] and the ELISA is carried out by antigen capture format [employing a second antibody].

Claim 9 is amended as follows:

9. (thrice amended) A method [for assessing neutralizing potency of an anti-serum against a toxin for which it is specific, said method] comprising

determining a neutralizing index given by the difference between

(1) a numerical assay value for a predetermined amount of [the] a toxin in [a predetermined amount of] a normal serum in a first test, and

(2) a numerical assay value for a mixture of the predetermined amount of the toxin plus a predetermined amount of [the] an antiserum specific for the toxin in a second test,

wherein the toxin assay is determined by ELISA test of the toxin plus normal serum in the first test;

and the toxin plus anti-serum assay is determined by ELISA test of the mixture of the toxin plus the anti-serum, such mixture containing a reduced amount of free toxin due to neutralization by the anti-serum, in the second test;

wherein an anti-LTNF comprising an antibody made

(1) against natural LTNF, or

(2) against a synthetic peptide consisting of at least five amino acids of the sequence

Leu Lys Ala Met Asp Pro Thr Pro Pro Leu Trp Ile Lys Thr Glu

is used as a reagent for the ELISA tests and reacts with free toxin in both the first test and the second test,

wherein the numerical assay values in both the first test and the second test are given by ELISA [binding affinity] color assay for anti-LTNF, and

wherein [for a given toxin,] an anti-serum having a higher neutralizing index is indicative of a greater potency for [the] that anti-serum against a given toxin.

Support: The amendment is fairly supported by Table VI, which shows a first run with venom plus normal serum and a second run with venom plus anti-serum for several venoms. The phrase "color assay for anti-LTNF" is fairly supported by Example VI, which states "The mixtures of venom with normal serum and specific anti serum were considered as antigens for ELISA. ELISA test was performed as described above" at page 16, lines 18-20, and Example II as pointed out hereinabove with respect to claim 7.